I. AMENDMENTS

In the claims:

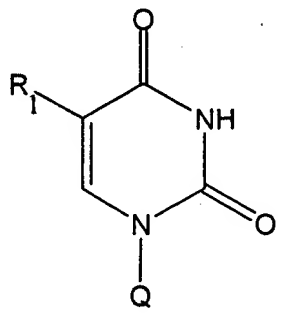
Cancel claim 1 without prejudice or disclaimer. Please amend claims 56 to 59, 62 and 76 as follows.

1. (Canceled).

56. (Currently Amended) A method for inhibiting the proliferation of a hyperproliferative cell, comprising contacting the cell with a 5'-phosphoryl or phosphoramidatyl substituted prodrug of a 5-substituted pyrimidine nucleoside or nucleotide, a derivative or a metabolite thereof that is selectively converted to a toxin in the cell by an endogenous, intracellular enzyme.

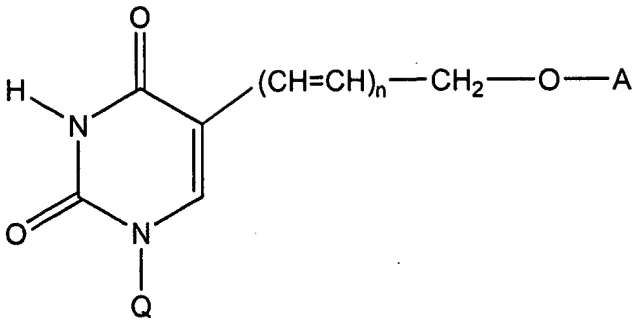
57. (Currently Amended) A method for treating a pathology characterized by hyperproliferative cells in a subject comprising administering to the subject a 5'-phosphoryl or phosphoramidatyl substituted prodrug of a 5-substituted pyrimidine nucleoside or nucleotide, a derivative or a metabolite thereof that is converted to a toxin in a hyperproliferative cell by an intracellular enzyme that is endogenously overexpressed or over-accumulated in the cell.

58. (Currently Amended) [A] The method of claim 56, wherein the prodrug, derivative or metabolite is ~~for inhibiting the proliferation of a hyperproliferative cell comprising contacting the cell with~~ an L- or D- isomer of the formula:

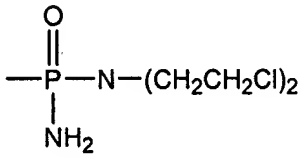


wherein R_1 is an electrophilic leaving group;

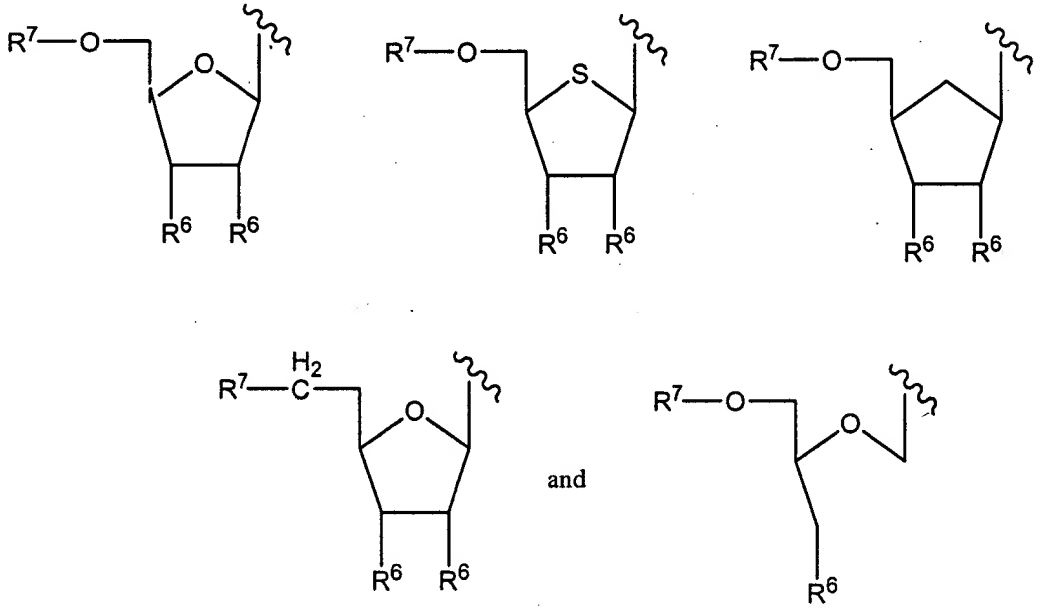
or a compound of the formula:



wherein n is an integer from 1 to 10; wherein A is a phosphoryl or phosphoramidatyl or a compound of the formula:



wherein Q is selected from the group consisting of:



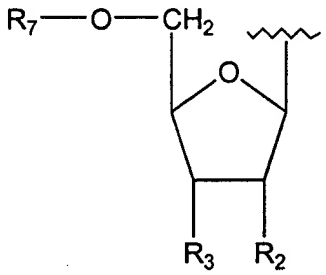
and

wherein R^6 is independently -H, -OH, -OC(=O)CH_3, or -O-Rg wherein Rg is a hydroxyl protecting group other than acetyl;

wherein R^7 is hydrogen, a masked phosphate group, or a phosphoramidatyl group.

~~a 5' substituted masked phosphoryl, a phosphoryl or phosphoramidatyl moiety selected from the group consisting of sugar; thio-sugar; carbocyclic; acyclic analogs and derivatives of a sugar, a thio-sugar or a carbocyclic; derivatives, analogs and pharmaceutically acceptable salts thereof.~~

59. (Currently Amended) The method of claim 58, wherein Q has the formula:

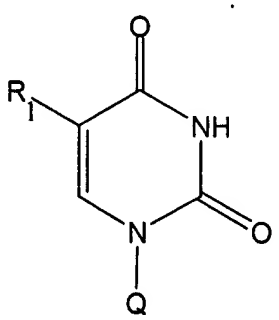


wherein R_7 is selected from the group consisting of a masked phosphoryl moiety~~,~~ and a phosphoramidatyl moiety, and wherein R_2 and R_3 are the same or different and are independently -H or -OH.

60. (Original Claim) The method of claim 58, wherein R_1 is a halogen.

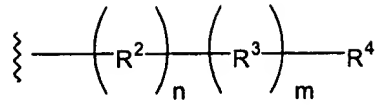
61. (Previously Amended) The method of claim 58, wherein R_1 is of the formula $(-CH=CH)_n-R_4$, wherein n is an integer from 1 to 10, and R_4 is selected from the group consisting of H, a halogen, alkyl, alkenyl, alkynyl, hydroxyl -O-alkyl, -O-aryl, O-heteroaryl, -S-alkyl, -S-aryl, -S-heteroaryl, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$, -NHCHO, -OCN, -SCN, $-N_3$, -NHOH, -NHO-alkyl, and $NHNH_2$.

62. (Currently Amended) A compound of the formula:



wherein:

R^1 is of the formula:



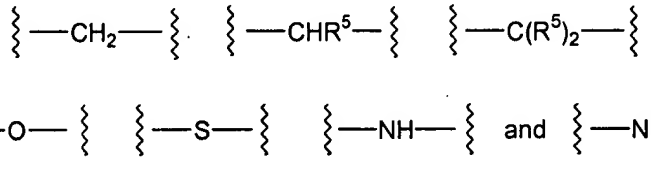
wherein ~~n is from 1 to 10 and~~ R^2 is <u>one of</u> ~~selected from the group consisting of:~~

an unsaturated hydrocarbyl;

an aromatic hydrocarbyl; ~~and,~~ <u>or</u>

a heteroaromatic;

R^3 is selected from the group consisting of:

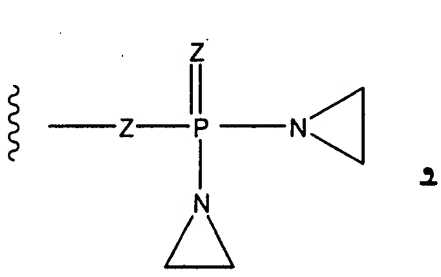


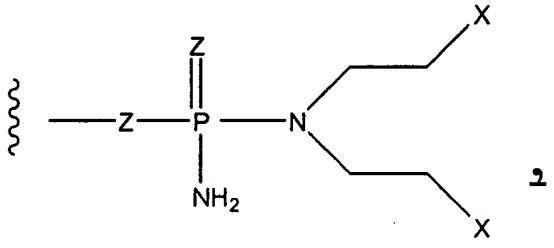
wherein R^5 may be the same or different and is independently a linear or branched alkyl group having from 1 to 10 carbon atoms, or a cycloalkyl group having from 3 to 10 carbon atoms;

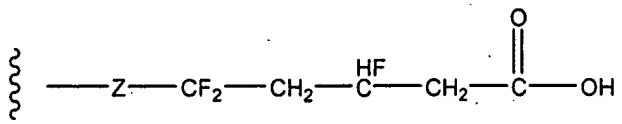
wherein n is an integer from 1 to 10;

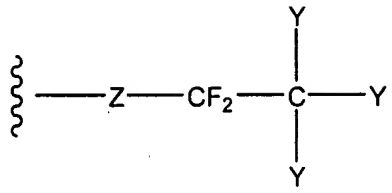
wherein m is 0 or 1;

wherein R^4 is a toxophore selected from the group consisting of:

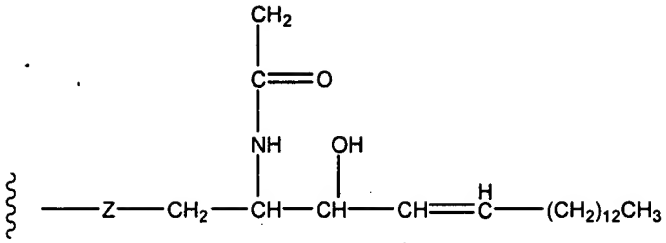




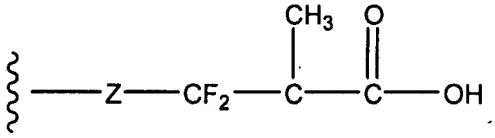




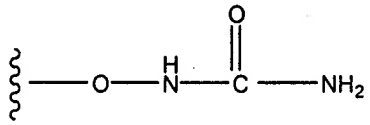
2



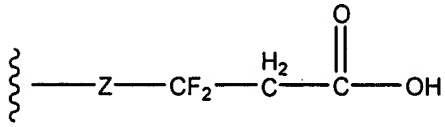
2



2



and



2

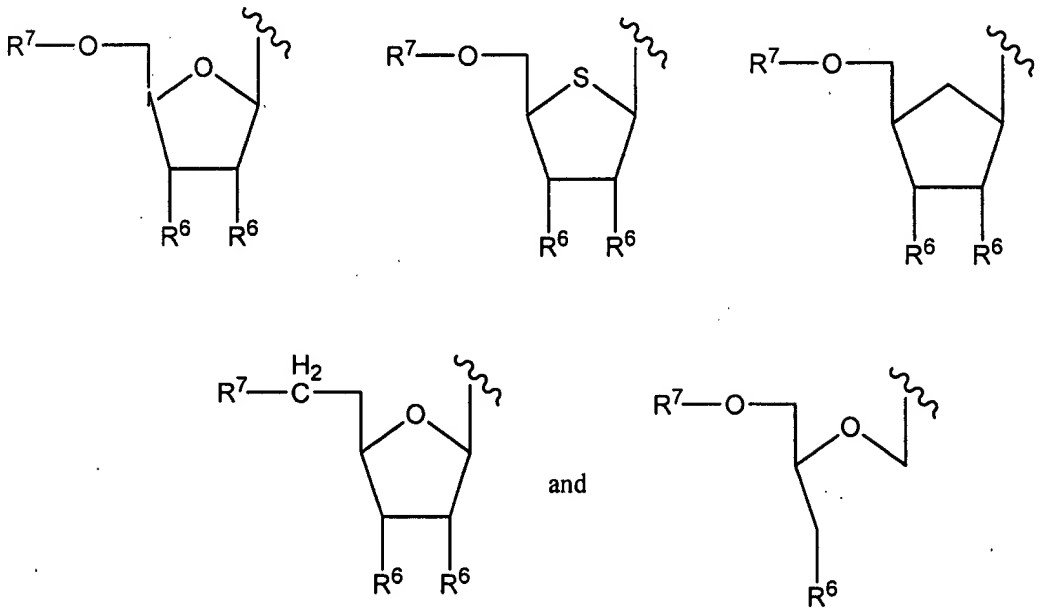
wherein X is -Cl, -Br, -I, or other potent leaving group, with the proviso that when R^7 is -H, and M is zero, then R^4 is not a halogen or when m is zero and n is zero, then

R^4 is not a halogen;

wherein Y is independently -H or -F;

wherein Z is independently -O- or -S-;

wherein Q is selected from the group consisting of:

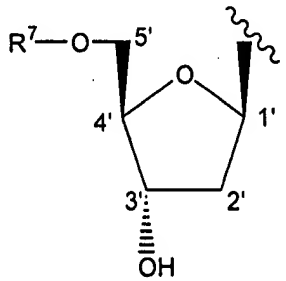


wherein R^6 is independently -H, -OH, $-OC(=O)CH_3$, or -O-Rg wherein Rg is a hydroxyl protecting group other than acetyl; and,

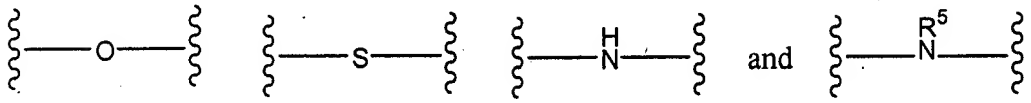
wherein R^7 is selected from the group consisting of hydrogen, a masked phosphoryl moiety and a phosphoramidatyl moiety ~~phosphate group, or a phosphoramidatyl group~~;

and wherein said compound may be in any enantiomeric, diasteriomeric, or stereoisomeric form, consisting of a D-form, L-form, α-anomeric form, and β-anomeric form.

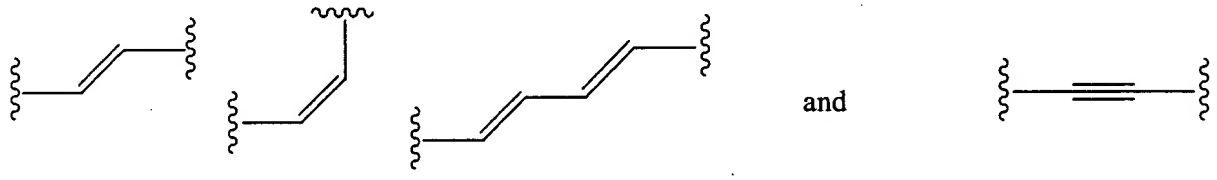
63. (Original Claim) A compound according to claim 62, wherein Q is:



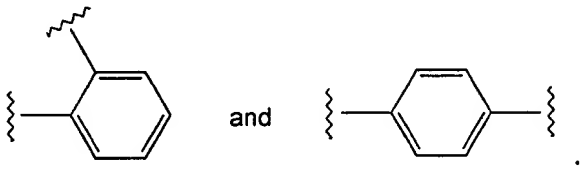
64. (Previously Amended) A compound of claim 62, wherein R^3 is selected from the group consisting of:



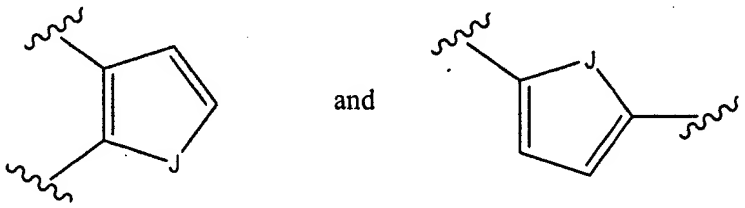
65. (Previously Amended) A compound of claim 62, wherein R^2 is selected from the group consisting of:



67. (Previously Amended) A compound of claim 62, wherein R^2 is selected from the group consisting of:

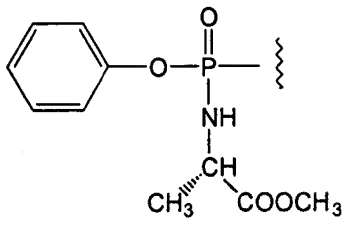


68. (Previously Amended) A compound of claim 62, wherein R^2 is selected from the group consisting of:

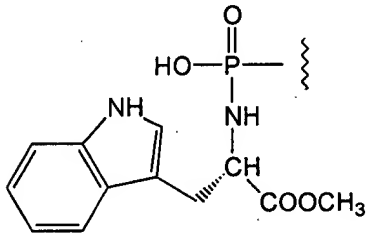


wherein J is -O-, -S-, -Se-, -NH-, or $-NR^{ALK}-$, wherein R^{ALK} is a linear or branched alkyl having 1 to 10 carbon atoms or a cycloalkyl group having 3 to 10 carbon atoms.

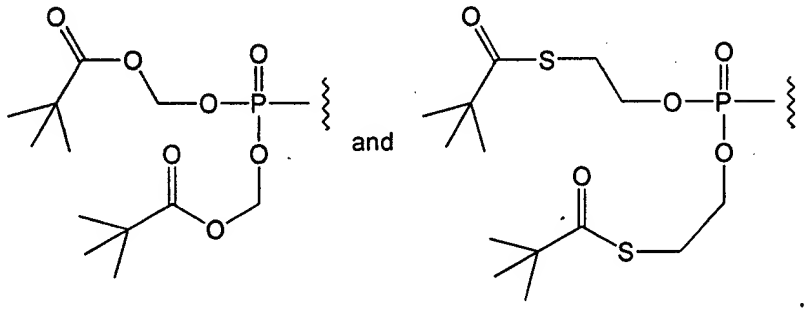
69. (Previously Amended) A compound of claim 62, wherein R^7 is:



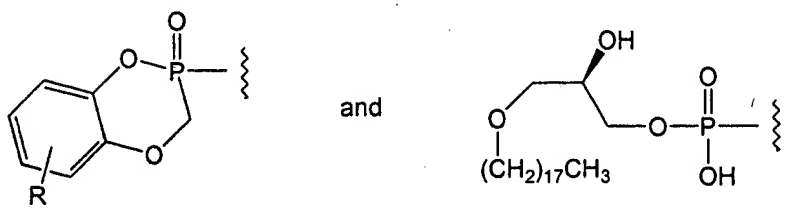
70. (Previously Amended) A compound of claim 62, wherein R^7 is:



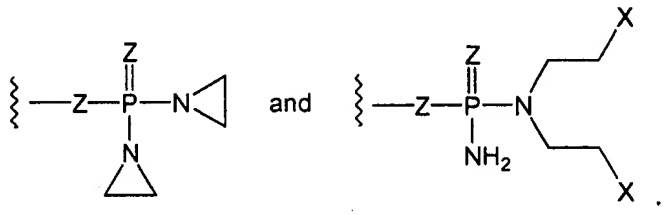
71. (Original) A compound of claim 62, wherein R^7 is selected from the group consisting of:



72. (Original) A compound of claim 62, wherein R^7 is selected from the group consisting of:

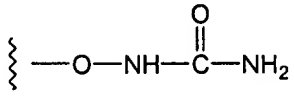


73. (Original) A compound of claim 62, wherein R^4 is selected from the group consisting of:

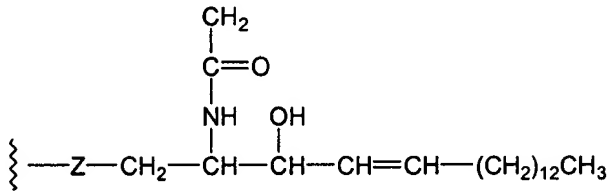


74. (Original) A compound of claim 62, wherein R^4 is selected from the group consisting of:

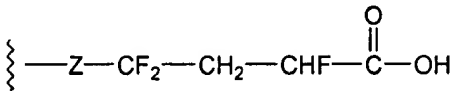
75. (Original) A compound of claim 62, wherein R^4 is:

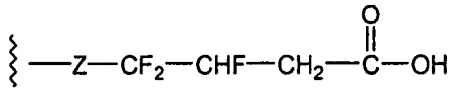


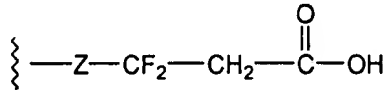
76. (Currently Amended) A compound of claim 62, wherein R^4 is:



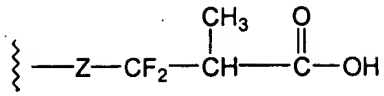
77. (Original) A compound of claim 62, wherein R^4 is:



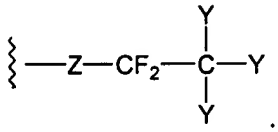




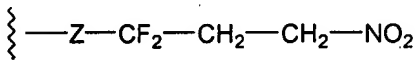
or



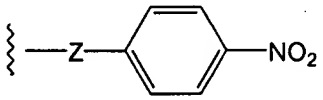
78. (Original) A compound of claim 62, wherein R^4 is:



79. (Original) A compound of claim 62, wherein R^4 is:



80. (Original) A compound of claim 62, wherein R^4 is:



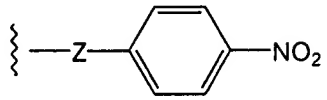
81. (Original) A method for inhibiting the proliferation of a hyperproliferative cell, comprising contacting the cell with an effective amount of a compound of claim 62.

82. (Original) The method of claim 81, wherein the hyperproliferative cell is characterized by the endogenous overexpression of an intracellular enzyme.

83. (Original) The method of claim 82, wherein the enzyme is thymidylate synthase.

84. (Original) A method for treating a pathology characterized by hyperproliferative cells in a subject comprising administering to the subject a compound of claim 62.

85. (Original) A method for screening for a therapeutic agent, comprising contacting a target cell with a compound of claim 62, wherein R^4 is:



86. (Previously Amended) A method of inhibiting the proliferation of a pathological cell that overexpresses an intracellular target enzyme, comprising:

(a) contacting the cell with a compound of claim 62; and

(b) allowing the cell to take-up and selectively convert the compound from an inactive state to an active toxic by-product by means of the intracellular target enzyme.

87. (Previously Amended) A method of inhibiting the proliferation of a hyperproliferative cell that overexpresses intracellular enzymes and which contribute to drug resistance, comprising:

(a) contacting the cell with the compound of claim 62; and

(b) allowing the cell to take-up and selectively convert the compound from an inactive state to an active toxic byproduct by means of the enzyme.

88. (Previously Amended) The method of claims 86 or 87, wherein the hyperproliferative cell is a cancer cell.